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SYNTHETIC COMMUNICATIONS, 19(9&10), 1661-1667 (1989)

SYNTHESES OF SUBSTITUTED 2-PHENYL

$\alpha\beta$ -UNSATURATED ALIPHATIC ACIDS

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Abstract-Additions of long chain aliphatic aldehydes in controlled basic media on 5-hydroxy 2-coumaranone or on 3-isochromanone give the corresponding ene-lactones (46-55%). Hydrolysis of the lactone ring leads to substituted 2-phenyl $\alpha\beta$ -unsaturated aliphatic acids from which stable K-salts or methyl esters were obtained.

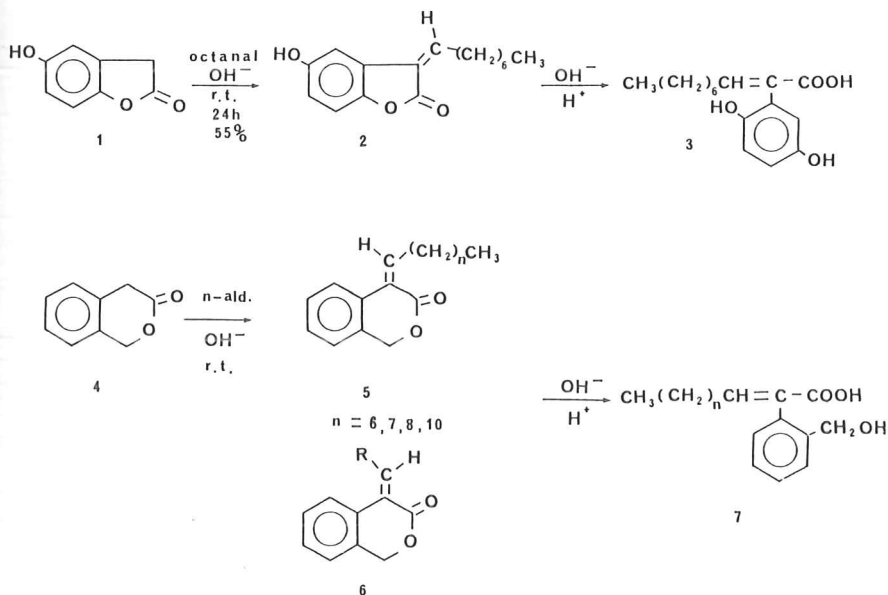
Aromatic aldehydes condense in controlled basic media on the methylene groups of lactones such as 5-hydroxy 2-coumaranone 1 and 3-isochromanone 4¹. This reaction occurs in competition with the opening of the lactone ring. By this procedure, a synthesis of Z-marginalin was recently reported². E-marginalin was previously³ isolated from the pygidial glands of the water beetle Dytiscus marginalis (Coleoptera). Substitutions carried out with methyl or ethyl aldehydes were not so satisfactory, leading to ene-lactones¹ which with time gave polymerized derivatives. The 5-OH group of 5-hydroxy 2-coumaranone 1 exerts an orientating force, on the intermediate secondary alcohols, as demonstrated by using p-nitro-benzaldehyde as reagent⁴. This phenomenon explains why

the Z-isomers are quantitatively obtained when carrying additions on the methylene group of 1. In agreement with Cram's rule, this effect is very likely combined with the stabilizing role of the interaction between the intermediate secondary alcohol function and the oxo group of the lactone ⁴. Similar additions carried out on 3-isochromanone 4 always gave mixtures of the corresponding E and Z isomers and these results corroborate our observation. Identification of both isomers was in this case rather simple, in particular because of the difference observed in ¹H NMR for the chemical shifts of the olefinic protons. Hydrolysis of the resulting ene-lactones gave stable K salts of the hydroxy-acids which could be transformed into methyl esters by action of diazomethane.

In the present publication, this reaction is extended to long chain aliphatic aldehydes leading to a new family of aryl substituted aliphatic $\alpha\beta$ -unsaturated acids.

Addition of n-octanal on 5-hydroxy 2-coumaranone 1 gave the Z-ene-lactone 2 isolated by preparative chromatography. Hydrolysis of the lactone ring of 2 lead to the $\alpha\beta$ -unsaturated acid 3 (K salt). This substance can also be considered as a new type of 2-substituted hydroquinone. By reactions of n-aliphatic aldehydes ranging from C₈ to C₁₂ with 3-isochromanone 4, mixtures of corresponding Z and E isomers of the ene-lactones 5 and 6 were obtained. Opening of the lactone ring lead to a series of 2-(2'-hydroxymethylphenyl)-enoic acids of

general structure 7 (racemization occurs during this transformation). It may be that the unstability of the free acids, contrasting with the lactones themselves, is bound to the bulky aryl substitution in position 2 of these aliphatic $\alpha\beta$ -unsaturated acids. This reaction appears to be of sufficient general use however for a direct access to a series of new compounds and is of particular interest in the case of 5-hydroxy 2-coumarone none due to the stereospecific formation of the Z-isomers. Due to chromatographical difficulties, we did not succeed as yet to separate the E and Z hydroxy-acid mixtures obtained from the hydrolysis of the E or Z ene-lactones (nor their corresponding methyl esters).



EXPERIMENTAL

General:Mp.:Kofler microscope,uncorrected;TLC:thin-layer chromatography on Schleicher-Schüll SiO₂ fluorescent films for analytical purposes,1mm thickness for preparative,UV observation at 254nm with a Desaga lamp, extractions from scrapped SiO₂ with ethyl acetate.¹H NMR on Bruker 200MHz, δ ppm,zero TMS;e.i.MS:AEI MS 50 spectrometer;UV:Perkin-Elmer lambda-5 automatic recorder.

Synthesis of the 2-aryl aliphatic ene-lactones 2,5,6:
general procedure:in a typical experiment,200mg of 3-isochromanone 4 (1.35mM) were dissolved in 25ml absolute ethanol at room temperature and 400mg of lauric aldehyde (2.14mM) added.A solution of KOH (1ml prepared from 100 mg in 15ml ethanol) was added dropwise under stirring. After 6h at 20°C,50ml ethyl acetate and 50ml water were added without saking,the organic phase was washed twice with water,dried over Na₂SO₄ and evaporated under vacuo. The product of this reaction was isolated by preparative TLC,giving 12mg (3%) of 5 (Rf 0.30) and 46mg (11%) of 6 (Rf 0.40),colourless oils,MS m/z 314.The repetition of this reaction for 24h lead to 11% of 5 and 30% of 6 (yields brought respectively to 12 and 36% after 72h reaction,overall yield 48%).UV λ max.,nm,ether,225 (7.3 x10³;256 (7.7x10³);¹H NMR:5: (CDCl₃),0.90,3H,t,CH₃;1.30,18H,m,CH₂;1.65,2H,q,CH₂ at C-3 of the chain;2.60,2H,dd,CH₂ at C-2 of the chain;5.20,2H,s,methylene of 3-iso-

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chromanone; 6.70, 1H, t, olefinic proton, J 7.5 Hz; 7.30-7.50, m, aromatic protons, 4H. Element. anal.: calc. for $C_{21}H_{30}O_2$ C 80.21 H 9.62%; found, 5, C 79.97 H 9.95; 6, C 79.85 H 9.53. The properties of the substances prepared starting from the aldehydes C_8, C_9, C_{10} were similar with all respects (except for MS in agreement with the corresponding molecular weights), the yields obtained after 72h at room temperature ranging between 36 and 40% for the Z isomers and between 10 and 20% for the E. All products were obtained as colourless oils and were characterized by MS, 1H NMR and element. anal., they all gave the same Rf values on TLC's as reported for the previous E and Z isomers. In the E series 6, the olefinic protons are found between 7 and 7.10 ppm in 1H NMR, in agreement with previous observations^{1,2} on products obtained from the addition of an aromatic aldehyde on 1 or 4.

The reaction of n-octanal on 5-hydroxy 2-coumaranone 1 in the same conditions, gave after 24h 55% of the Z-ene-lactone 2, and no E isomer could be noticed as previously observed in the case of the addition of aromatic aldehydes. 2 was isolated by preparative TLC, Rf 0.60 in hexane-ethyl acetate 1:1 and was crystallised from ethyl acetate-hexane, m.p. 129-131°C, yellow microprisms, MS m/z 260, 1H NMR ($CDCl_3$), 0.90, t, 3H, CH_3 ; 1.30, m, 8H, CH_2 ; 1.62, q, 2H, CH_2 at C-3 of the aliphatic chain; 2.65, q, 2H,

CH_2 at C-2 of the chain; 6.75, dd, 1 H, olefinic proton;

aromatic protons:7.3-7.5,4H;In this series,the olefinic protons resulting from the addition of aromatic aldehydes^{1,2} were previously found between 6.70 and 6.80ppm. Element.Anal.:calc. for $C_{16}H_{20}O_3$ C 73.82 H 7.74%;found C 73.76 H 7.85.

Substituted 2-phenyl 2-enoic acids and their derivatives,general procedure from the lactones 2,5,6.Hydrolysis of the lactones 2,5,6,was readily obtained by treatment of methanol solutions (room temp.) by theoretical amounts of NaOH (2h) and acidification by dilute HCl previous to extraction by ether.Methyl esters were obtained from these acids by the short action of an ether solution of diazomethane (colourless oils,homogenous in TLC,Rf 0.65,hexane-ethyl acetate 7:3).In spite of this homogenous behaviour on TLC,these methyl esters are mixtures of E and Z isomers as indicated by the complexity of the signals observed in NMR between 6.70 and 7.50ppm. This observation was confirmed by the relactonization of the acids by gentle warming of methanol solutions in presence of traces of HCl (water-bath at 60°C) giving back mixtures of E and Z lactones whatever was the starting material.Stable K-salts were obtained from these lactones 5,6 by proceeding with theoretical amounts of K_2CO_3 and bringing the methanol-water solutions to dryness under vacuo (microcrystalline powder).Acidification of these K salts by dilute HCl and further extraction by

ether followed by esterification with diazomethane, gave the same mixtures of isomers as mentioned above. (All methyl esters were checked by MS and ^1H NMR and gave the expected data).

The new products mentioned in this publication were systematically assayed on the germination of water-cress seeds for research of an eventual biological activity but at a concentration of $200\mu\text{g/ml}$ the results were found negative in all cases.

The aldehydes and 3-isochromanone were from Fluka AG. (Switzerland) and 5-hydroxy 2-coumaranone was an Aldrich-Europe product.

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This publication is dedicated to the memory of the late Professor Edgar Lederer (1908-1988).

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